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**WO 01/39582 A1**

(54) Title: USE OF A BUFFER TO PREVENT CANDIDA ALBICANS INFECTIONS ON THE SKIN

(57) Abstract: The present application relates to using an ingredient capable of buffering within the pH range 2.0 - 5.5, for preparing a skin-occlusive or mucous membrane-occlusive article for preventing skin irritations and lesions caused by *Candida albicans*. Examples of such articles are absorbent articles, such as diapers, pantyliners and sanitary napkins, wound dressings, such as bandages, surgical tapes and plasters, and finally gloves, prostheses and indwelling catheters.

Use of a buffer to prevent *Candida albicans* infections on the skin.

The present application relates to using a substance capable of buffering within the pH range 2.0 - 5.5, for preparing a skin-occlusive or mucous membrane-occlusive article for preventing skin irritations and lesions caused by *Candida albicans*. Examples of such articles are absorbent articles, such as diapers and sanitary napkins, wound dressings, such as bandages surgical tapes and plasters, gloves, prostheses and indwelling catheters.

10      Introduction

Infections caused by *Candida albicans* may constitute a major problem in connection with using skin-occlusive, mucous membrane-occlusive and absorbent articles such as diapers, pantyliners, sanitary napkins and wound dressings. *Candida albicans* has been found to correlate with severity of diaper dermatitis (Benjamin L, Pediatrician 1987, suppl. 1, p. 21 - 26). There are investigators that give *C. Albicans* a primary causative role in some expressions of diaper dermatitis (Leyden J and Kligman AM, Arch. Dermatol. 1978, vol 114, p. 56 - 59).

20      pH appears to be a major source of confusion and contradiction in the context of *Candida* ecology. *Candida* carriage *in vivo* can occur readily over a broad range of pH. pH may be a factor of significance in the pathological status of *C. albicans* *in vivo*, but it does not exert its influence by affecting growth of the fungus, i.e. the rate of increase of its biomass (Odds FC, Candida and Candidosis. A review and bibliography. 2<sup>nd</sup> ed. 1988, Bailliere Tindall). Dimorphism, the ability of *C. albicans* to exist in a blastospore and a filamentous form, is reported to be influenced by pH (Buffo et al., Mycopathologia, vol. 85 (1984), p. 21-30; Odds (1988), *supra*). The blastospore form is favoured by slightly acidic pH and the filamentous form at neutral pH or above. Furthermore, it has been shown that microfilaments play an important role during pH-regulated morphological transition (Yokoyama et al., Microbiology, vol. 140 (1994), p. 281-287). Clinical observations of diabetic patients,

where a higher skin surface pH is possibly correlated to candidal intertrigo, have been reported (Yosipovitch et al., Diabetes Care, vol. 16 (1993), p. 560-563). As already mentioned, there is often a risk for infections, skin irritations and lesions when covering the skin or mucous membranes with absorbent articles, wound dressings, plasters, gloves, prostheses and like articles. WO 98/57677 and EP 0 202 126 both disclose that a neutral or a slightly alkaline pH in connection with using absorbent articles may lead to skin irritation and problems with odorous substances. According to the documents these problems are caused by lipases and proteinases present on the skin and the problems can be overcome by decreasing the pH of the absorbent article. The documents do not give any particular information about problems caused by *Candida* or how to reduce the virulence of *Candida albicans*.

#### Summary of the invention

Now it has turned out that the virulence capability of *Candida albicans* can be substantially impaired by decreasing pH of a skin-occlusive or mucous membrane-occlusive article to a value within the range from 2.0 to 5.5. Thus a skin-occlusive or mucous membrane-occlusive article such as an absorbent article (a diaper, a sanitary napkin, a pantyliner or a wound dressing, such as a bandage), a plaster, a surgical tape, said article containing a pharmaceutically acceptable non-toxic and non-irritating substance capable of buffering within the pH range 2.0 - 5.5, is used to for preventing skin irritations and lesions caused by *Candida albicans*.

#### Detailed description of the invention

Accordingly, the present invention relates to using an ingredient capable of buffering within the pH range 2.0 - 5.5, for preparing a skin-occlusive article for preventing skin irritations and lesions caused by *Candida albicans*. Any pharmaceutically acceptable, non-toxic and non-irritating ingredient capable of buffering within the specified range can be used. Examples of suitable buffering ingredients are superabsorbent particles showing a level of neutralisation within the range of 20 - 50 %,

and pharmaceutically acceptable, non-toxic and non-irritating buffering solutions, such as organic salt buffering solutions, for example an acetate buffer or a citrate buffer. The buffering solution can be directly added to the skin-occlusive or mucous membrane-occlusive article. Alternatively, a pharmaceutically acceptable gel containing the buffering solution can be added. Examples of suitable gels include gels normally used for pharmaceutical purposes, such as agarose.

An acid buffering substance according to the present invention is added to a skin-occlusive article. As disclosed herein, the terms "skin-occlusive article" or "mucous membrane-occlusive article" relates to an article, which is intended to cover the skin or mucous membranes of a person. A skin-occlusive article or mucous membrane-occlusive article according to the present invention can be an absorbent article, such as a diaper, a sanitary napkin, a pantyliner or a wound dressing, a surgical tape, a plaster, gloves, prostheses or indwelling catheters. It is not critical for the invention how the acid buffering substance is added, and accordingly it can be added to the skin-occlusive article in many different ways. Examples of suitable methods for adding the acid buffering substance to the skin occlusive article are administration of a solution containing the acid buffering substance, or administration of said substance as a powder or gel. The administration can be carried out in connection with manufacturing said article or after said article has been manufactured.

As disclosed herein, the term "pharmaceutically acceptable antifungal agent" relates to compounds normally used to treat *Candida* infections, such as imidazole derivatives, nystatin and ciclopirox olamine. These compounds are added to the skin-occlusive or mucous membrane-occlusive article in amounts corresponding to common therapeutical doses.

The present invention will now be described with reference to the enclosed figures and tables, in which:

Figure 1 shows an example of a diaper to which an acid buffering substance can be added in accordance with the invention;

5       Figure 2 discloses the natural distribution of skin surface pH on volar forearms in 15 females. The observations are mean values of left and right arm;

10      Figure 3 presents a diagram showing pH development of patch sites before, during and after wearing a patch buffered with an acid buffering substance and a regular reference patch;

15      Table I presents results from visual assessment of skin reaction to *Candida albicans* infection; and

20      Table II shows growth of *Candida albicans* 24 hours after inoculation.

15      The diaper 100 disclosed in figure 1 comprises a liquid-permeable outer layer 1, for example made of a fibre fabric or a perforated plastic film, a liquid-impermeable outer layer 2, for example made of a plastic film or a hydrophobic fibre fabric, and finally an absorbent body 3 enclosed between the outer layers 1, 2.

20      The diaper is intended to surround the lower part of the trunk of the wearer like a pair of absorbing pants. It is therefore designed with two end parts 4, 5 as well as a narrower crutch part 6 between the end parts, which when the diaper is used is intended to be arranged in the crutch of the wearer between the legs. In order to obtain the desired pant design, adhesive flaps 7 are arranged close to the rear waist edge 8. Upon use, the adhesive flaps are fastened to the front part 5 of the diaper, close to the front waist edge 9, in order to hold the diaper together around the waist of the wearer.

30      Moreover, the diaper according to figure 1 comprises pretightened elastic means 10, which may consist of elastic strings, elastic threads, elastic foam or another suitable

material. The elastic means 10 are, for the sake simplicity, shown in outstretched condition. However, as soon as the stretching ceases they contract and form elastic bands in the diaper.

- 5      The absorbent body 3 in the example shown in figure 1 is formed by two layers 11,12, an upper liquid-receiving layer 11 and a lower layer 12 which spreads and distributes the liquid. The upper liquid-receiving layer must quickly be able to receive a large amount of liquid within a short amount of time, i.e. have a higher instantaneous liquid absorption capability, but the lower storage and distribution layer 10      12 must have a high liquid distribution capability and be able to drain liquid out from the receiving layer 11 and distribute this liquid in the storage and distribution layer 12. The differences between the layers 11, 12 can be accomplished by density differences. A more compressed fibre structure distributes the liquid better than a corresponding fibre structure having a lower density. Such a low-density structure 15      has a higher instantaneous liquid absorption capability and a lower distribution capability due to its larger pore size. Different absorption capabilities can also be achieved by using different fibre structures having different characteristics. Thus chemically produced cellulose fluff pulp shows better distribution characteristics compared to, for instance, mechanically or chemi-thermomechanically produced 20      pulp, such as chemi-thermomechanical pulp (CTMP). A fibre structure containing chemically stiffened cellulose fibres shows a higher instantaneous liquid absorption ability but a lower distribution ability compared to conventional chemical pulp. Other materials suitable as receiving layers 11 can be a wadding of natural fibres or 25      a fluffy nonwoven material.
- A partially neutralised superabsorbent is admixed in the upper liquid-receiving layer 11 of the absorbent body 3. This superabsorbent act as a acid buffering substance in accordance with the present invention.
- 30      A conventional superabsorbent is admixed in the lower liquid storage and distribution layer 12 of the absorbent body. It is advantageous to put a conventional super-

absorbent in the lower liquid storage layer 12, because a conventional superabsorbent has a higher total absorption capacity compared to a partially neutralised and pH-regulating superabsorbent.

- 5      Naturally, the invention also comprises other embodiments of the absorption body. The absorbent body may contain both partially neutralised superabsorbents and conventional superabsorbents, and both the superabsorbents can be equally distributed in both the upper and lower absorbent layers. Moreover, except for cellulose fluff pulp it is possible to only include one kind of superabsorbent material. In that  
10     case, the superabsorbent material also acts as a pH-regulating substance in accordance with the present invention.

#### Experimental work

- 15     A study was carried out in order to determine whether different environmental pH affects *Candida* infections on skin. Fifteen female, healthy volunteers between 30 and 63 years of age (average 44.5 years) participated. The following routine procedures and materials were used:
- 20     The experimental patches were made of common diaper materials and punched out as circular disks with a diameter of 70 mm. The outer side of polyethylene and the inner side (that will be placed towards the skin) of nonwoven polypropylene were glued together with a 10 mm edge around the inner circular core of 50 mm diameter. The inner core consisted of approximately 0.85 g cellulose pulp and approximately  
25     0.15 g of superabsorbent polymer (IM 7100 and E127/97, Clariant GmbH, DE). The superabsorbent polymer was a polyacrylic acid, which was adjusted to either pH 4.5 or 6.0. It acts as a strong buffering system.  $10^4$  cells per ml *C. albicans* were suspended in a physiological saline solution. 7 ml of this solution was added to each patch, 15 minutes before they were attached to the forearms.

Skin surface pH was measured with a Courage+Khazaka PH900, Mettler-Toledo flat electrode 304. Every morning and afternoon the instrument was calibrated at pH 4.0 and 7.0. The instrument accuracy is 0.1 units. A few drops of deionized water was added to the electrode before measurement and the average of three values was recorded.

The *C. albicans* strain used was type H29, kindly provided by Professor Lars Edebo, Department of Microbiology, Sahlgrenska University Hospital, Göteborg, SE. Cells were grown on Sabouraud's glucose agar at 37°C for 24 hours before use.

A modification of the Williamson-Kligman scrub technique was used for assessment of the resident skin microflora and the added *C. albicans*. A stainless steel ring with an internal diameter of 2.6 cm and covering a skin area of 5.5 cm<sup>2</sup> was used. One millilitre of sterile 0.075 M phosphate buffer (pH 7.9) containing 0.1% Triton X-100 was poured into the ring, and the skin was gently rubbed with a blunt sterile glass rod for one minute and the fluid was removed with a Pasteur pipette (Faergemann J. Mapping the Fungi of the Skin. Handbook of Non-invasive Methods and the Skin, chapter 10.2, CRC Press, 1995). Serial dilutions were performed in PBS and samples from the dilutions were plated out. Plates were incubated at 37°C and read after 48h.

The paired t test was used to test for statistical significance between pH differences, differences in number of *Candida* organisms. The differences in observed skin lesions were tested by a sign test.

At the start of the trial, skin microflora was determined with the scrub test. All subjects had coagulase-negative *Staphylococci* (range 170-25000 colony-forming units (cfu)). Two of the subjects had *Diphtheroid* sp (range 50 -2400 cfu). Four subjects had *Bacillus* sp (range 10-1200 cfu). One subject had *S. aureus* on one arm (10 cfu).

The amounts are given in colony-forming units per 5.5 cm<sup>2</sup> skin. No growth of *C. albicans* was found in any subject before the trial.

5 The skin surface pH of the 15 volunteers was measured at the start and varied between 4.5 and 6.0. The mean value was 5.2. The results are shown in figure 2.

Patches preloaded with a *Candida* suspension (10<sup>4</sup> cells/ml) were taped to the forearms of the volunteers. The patches had two different pH-values and were randomly placed on either left or right arm. The patches were worn under strict occlusion for  
10 24 hours. The patches were removed, and after approximately 2 minutes pH values of the skin was measured. When the patches were removed after 24 hours of occlusion the pH was 5.1 +/- 0.18 and 5.7 +/- 0.29 (mean +/- SD) at the two respective sites. The difference is statistically significant at p<0.0001. The skin was visually examined and was sampled to determine the number of cfu of *Candida* in an area of  
15 5.5 cm<sup>2</sup>. The summarised results are shown in table II. No statistically significant difference (P=0.64) was found between the "acidic" site and the reference site. Growth was found on both arms in 13 subjects. In one subject growth was found only on the "acidic" site, and in one subject only on the reference site.  
  
20 After 48 hours, the pH measurements as well as the *Candida* sampling were repeated. The results of the pH measurements are disclosed in figure 3. The results of the *Candida* samplings after 48 hours, i.e. 24 hours after the patches had been removed and the lesions had become visually evident, show that 9 subjects had no growth at all of *C. albicans*. Three subjects showed low numbers (10-130 cfu) and  
25 one subject had an increased growth since the day before (1400 and 4300 cfu on respective arms). Two subjects were missing on this occasion, and accordingly no microbial data could be obtained.

30 The skin lesions were visually assessed. No reaction = 0; faint reaction = 1; evident reaction = 2; strong reaction = 3. The reading was blinded and the patch type unknown to the assessor. The skin reactions were also recorded on photographs. This

visual assessment of skin reactions gave a very clear result. The acidic site had less severe reactions than the reference site in all 14 subjects that reacted. The sign test shows a statistically significant difference at  $p<0.001$  for difference in reaction at the two sites. The detailed result is presented in table I.

5

Consequently, the pH-induced differences turned out not to be due to inhibited growth of *Candida albicans*. They are probably due to a pH influence of the virulence capacity of the fungus and/or an improvement of the host's defence ability.

## Claims

- 5 1. Use of a pharmaceutically acceptable, non-toxic and non-irritating ingredient capable of buffering within the pH range 2.0 - 5.5, for preparing a skin-occlusive article or a mucous membrane-occlusive article for preventing skin irritations and lesions caused by *Candida albicans*.

10 2. Use of a pharmaceutically acceptable, non-toxic and non-irritating ingredient capable of buffering within the pH range 2.0 - 5.5, together with a pharmaceutically acceptable antifungal agent such as an imidazole derivative, nystatin and ciclopirox olamine, for preparing a skin-occlusive article or a mucous membrane-occlusive article for preventing skin irritations and lesions caused by *Candida albicans*.

15 3. Use according to claim 1 or claim 2, characterised in that the pharmaceutically acceptable, non-toxic and non-irritating buffering ingredient is a partially neutralised superabsorbent.

20 4. Use according to claim 1 or claim 2, characterised in that the pharmaceutically acceptable non-toxic and non-irritating buffering ingredient is an organic acid salt buffering solution.

25 5. Use according to anyone of claims 1 - 4 for preparing a skin-occlusive or mucous membrane-occlusive article, which is an absorbent article such as a diaper, a sanitary napkin, or a pantyliner.

6. Use according to anyone of claims 1 - 4 for preparing a skin-occlusive or mucous membrane-occlusive article which is a wound dressing, a plaster, a surgical tape, or a like article.

7. Use according to anyone of claims 1 – 4 for preparing a skin-occlusive article or a mucous membrane-occlusive article, which is a glove, a prosthesis, or an in-dwelling catheter.

1/5

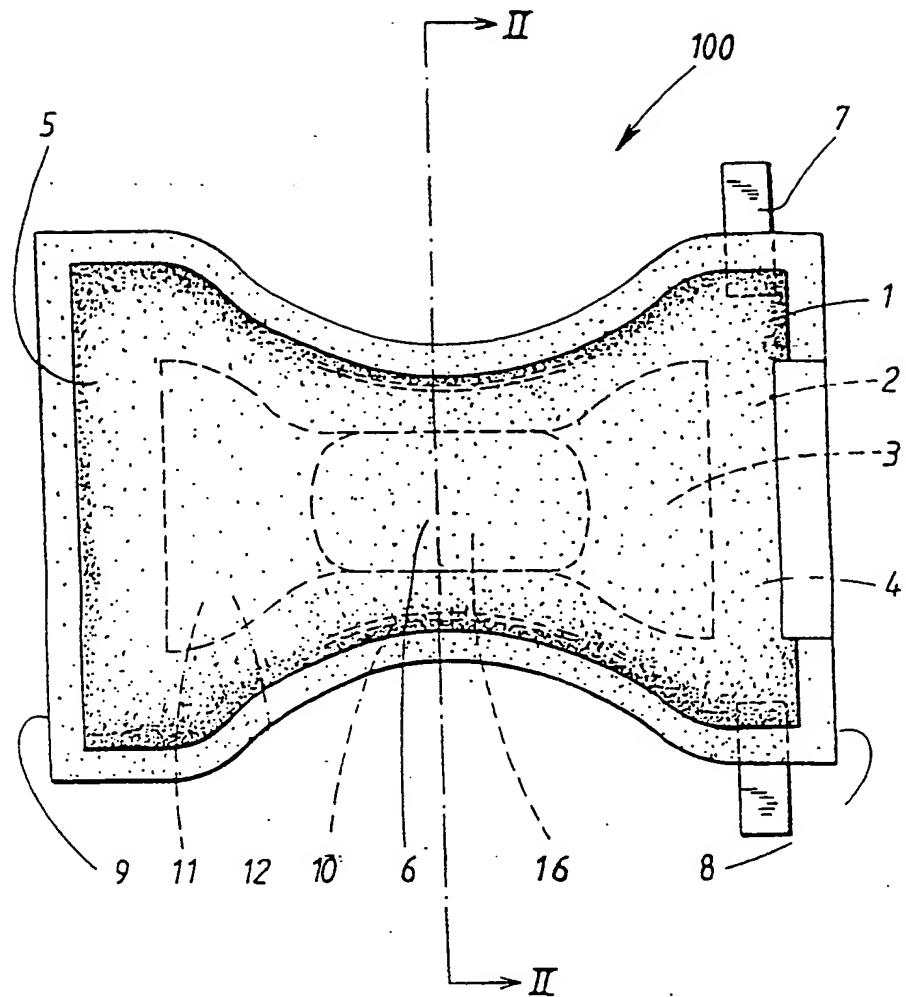
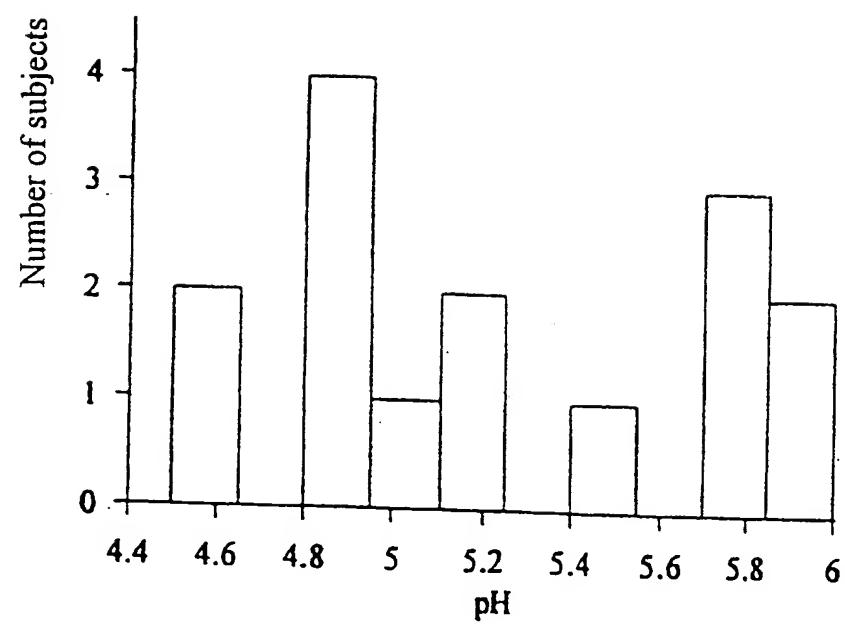


FIG. 1

Substitute sheet (Rule 26)

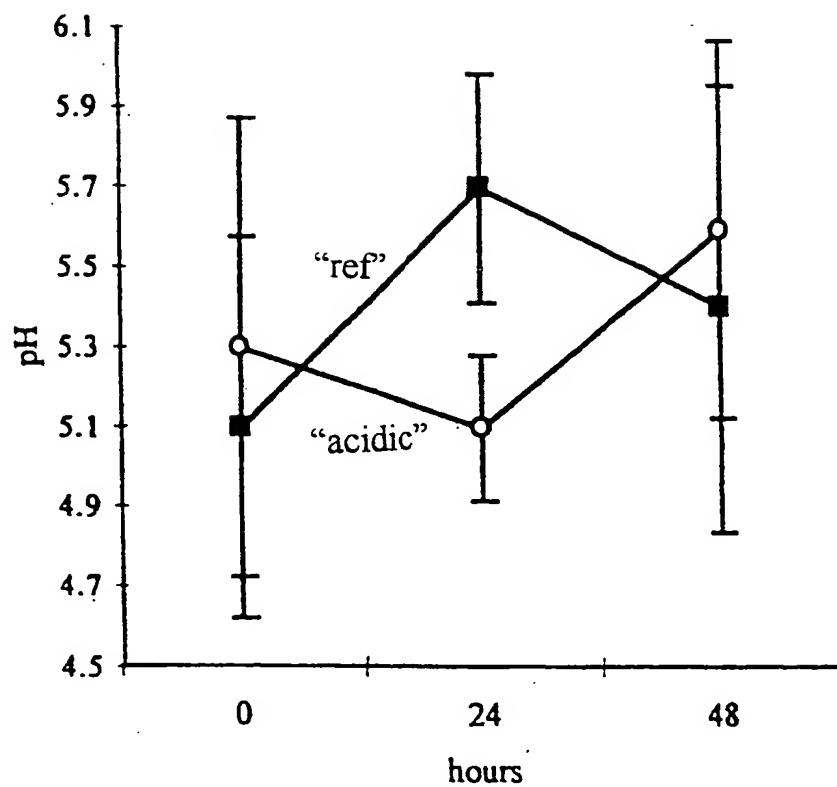
2/5

FIG. 2



3/5

FIG. 3



4/5

Table I. Visual assessment of skin reaction to  
*Candida albicans* infection

Reaction	Number of subjects	
	"low" pH	"high" pH
No reaction (0)	12	1
Faint (1)	3	5
Evident (2)	-	5
Strong (3)	-	4

5/5

Table II. Growth of *Candida albicans* 24 hours after inoculation

	“low” pH	“high” pH
cfu (mean)	974	813
SD	1548	907
max	6000	3000
min	0	0

## **INTERNATIONAL SEARCH REPORT**

International application No.

PCT/SE 00/02165

#### A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 15/42

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

**Minimum documentation searched (classification system followed by classification symbols)**

IPC7: A61L, A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ, NPL, MEDICINE

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0311344 A2 (THE PROCTER & GAMBLE COMPANY), 12 April 1989 (12.04.89)  --	1-7
Y	GB 2326348 A (SCA MÖLNLYCKE AB), 23 December 1998 (23.12.98), see specially abstract, line 6  --	1-7
A	Diabetes Care, Volym 16, Nr 4, April 1993, Gil Yosipovitch, md et al, "Skin Surface pH in Intertriginous Areas in NIDDM Patients. Possible correlation to candidal intertrigo", page 560 - page 563, see specially the finish, page 562  --	1-7

Further documents are listed in the continuation of Box C.

See patent family annex.

- \* Special categories of cited documents
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - "&" document member of the same patent family

Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 00/02165
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## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0202126 A2 (THE PROCTER & GAMBLE COMPANY), 20 November 1986 (20.11.86), see abstract  --	1-7
A	WO 9519190 A1 (GRAZIANI, CARLO, ALFREDO), 20 July 1995 (20.07.95), see abstract  --	1-5
A	Arch Dermatol, Volym 114, Januari 1978, James J. Leyden, md et al, "The Role of Microorganisms in Diaper Dermatitis" page 56 - page 59  -----	1-5

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.	
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